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Recent Advances in the Pathophysiology of Asthma

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THE CLASSIC CONCEPT OF BRONCHIAL ASTHMA as a disease of solely immunologic nature cannot explain many phenomena frequently associated with asthma: hyperresponsiveness of the tracheobronchial tree to chemical mediators and irritants; exacerbations produced by certain respiratory infections, emotional and physical factors; the presence of eosinophilia; decreased bronchodilator response to epinephrine in patients with status asthmaticus; and the therapeutic response of agents which restore beta adrenergic responsiveness. In addition, a large number of asthmatic patients have no evidence of any reaginic (immunoglobulin E) abnormality.

Neuropharmacology

Beta Adrenergic Blockade Theory[1]

The tone of the airways is modulated in large part by the balance of adrenergic and cholinergic activity upon bronchial smooth muscle (Table 1). Adrenergic stimulation leads to bronchodilatation if beta receptors (dominant in lung) are activated and to bronchoconstriction when alpha receptors are stimulated, while cholinergic stimulation results in bronchoconstriction. Recently, the beta adrenergic receptor has been further dissected into beta 1 (cardiac stimulator) and beta 2 (bronchodilator and vasomotor depressor) sub-groups.[2] This has important therapeutic implications since use of drugs which selectively cause bronchodilatation has obvious advantages.

In the early 1960's Szentivanyi advanced the theory of beta adrenergic blockade as a possible unifying pathogenic mechanism in asthma.[1] In brief, this theory proposes that many of the stimuli which result in the clinical syndrome of asthma do so by causing release of potent chemical mediators of inflammation (discussed further below) such as the kinins, slow reacting substance of anaphylaxis (SRS-A), histamine, serotonin and acetylcholine. These mediators, in turn, result in both bronchoconstriction and secretion of epinephrine as a homeostatic response. If beta adrenergic receptors are normally responsive, activation of these by epinephrine will balance concurrent alpha adrenergic and cholinergic receptor stimulation and airway patency will be maintained. However, if beta receptors are defective, bronchoconstriction is favored. Through experimentation first with hypothalamically imbalanced guinea pigs and later with mice challenged with Bordetella pertussis, Szentivanyi presented evidence

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TABLE 1.—*Pharmacology of Autonomic Modulation*

Reactant	*Site of Action*	*Cyclic Nucleotide Effect*	*Mast Cell Mediator Release*	*Bronchial End Organ Response*	*Blocker*
Isoproterenol	Beta Adrenergic Receptor-Adenyl Cyclase Stimulation	↑cAMP	Inhibited	Bronchodilatation	Propanalol
Epinephrine*	Beta Adrenergic Receptor-Adenyl Cyclase Stimulation	↑cAMP	Inhibited	Bronchodilatation	Propanalol
Norepinephrine	Alpha Adrenergic Receptor ?ATPase Stimulation	↓cAMP	Enhanced	Bronchoconstriction	Phentolamine
Theophylline	Phosphodiesterase Inhibition	↑cAMP	Inhibited	Bronchodilatation	..
Acetylcholine and analogues	Cholinergic Receptor-?Guanyl Cylase Stimulation	↑cGMP	Enhanced	Bronchoconstriction	Atropine

*Also has adrenergic activity but, in the lung, beta is dominant.

which demonstrated that creation of autonomic imbalance (decreased beta adrenergic receptor function with normally intact alpha adrenergic and cholinergic receptor function) could produce many of the immunologic, pharmacologic and biochemical abnormalities noted in asthmatic patients.[1]

The evidence for generalized beta blockade in asthma includes metabolic, pulmonary and hematologic changes. *Metabolic* studies have demonstrated less elevation of serum glucose, lactate and pyruvate following administration of the beta stimulants isoproterenol and epinephrine in asthmatics when compared with normal subjects, this decreased activity was related to severity of disease.[3,4] The beta-blocking agent propanalol has several interesting *pulmonary* effects; two of these are quite important; development of increased airway resistance following administration in the asthmatic,[5] and production of similar findings in patients with allergic rhinitis without clinical asthma following challenge with either inhaled antigen or the cholinergic stimulant, mecholyl (these agents are not usually capable of producing brochospasm when administered alone to these patients).[6,7] Two important *hematologic* observations have also been made. The eosinopenic effect of the catecholamines is lessened in the asthmatic, as well as in propanalol-blocked normal subjects, suggesting spontaneous beta blockade effect in the asthmatic.[8] Lymphocytes from patients with severe, active asthma[9] and atopic dermatitis[10] have significantly less cyclic AMP (cAMP) before and after isoproterenol stimulation than do lymphocytes from normal subjects. Cyclic AMP is a substance produced in cells by beta stimulation (see below). In some cases cAMP levels rose to normal as improvement in clinical status of asthma occurred, suggesting that beta blockade may be an acquired rather than a congenital defect.[9] Proof of this latter suggestion will require measurement of cAMP in the target organs themselves.

These concepts are also useful in understanding the effects of treatment. It is necessary, however, to first briefly review the concept of the "second messenger" proposed by Sutherland.[11,12] According to this hypothesis, a hormone (first messenger) reacts with a receptor on the target cell membrane, resulting in activation of the enzyme adenyl cyclase, which is thought to be the beta adrenergic receptor. This membrane-bound enzyme is found in all mammalian cells, except the non-nucleated red cell. It catalyzes the conversion of adenosine triphosphate (ATP) to cyclic 3′, 5′ adenosine monophosphate (cAMP), the second messenger, a nucleotide with broad biological function. cAMP is degraded by the enzyme phosphodiesterase to the inactive 5′ AMP. It has been found that several of the agents useful in treatment of asthma increase intracellular cAMP either by adenyl cyclase stimulation (for example, catecholamines) or by inhibition of phosphodiesterase (methyl xanthines for example). Accumulation of cAMP leads, in turn, to bronchial smooth muscle relaxation and inhibition of lung mast cell release of several mediators including histamine and SRS-A.[13] Szentivanyi has suggested that the abnormality common to all asthmatics may be defective airway adenyl cyclase (beta receptor) resulting in decreased amounts of the second messenger cAMP.[1] The resulting chemical disturbance produces, in turn, autonomic imbalance favoring bronchoconstriction. The basis for

other forms of atopic disease has been postulated to be localized deficiencies of adenyl cyclase in nasal tissue (allergic rhinitis) and skin (atopic dermatitis).[1]

The Irritant Cough Receptor—"Twitchy" Lung Syndrome

Many noxious stimuli such as citric acid, charcoal and cold air inhalation result in bronchoconstriction, presumably by stimulation of subepithelial cough receptors.[14] The pathways are mediated by the vagus and can be blocked by previous administration of atropine.[14] Since asthmatic subjects have increased sensitivity to these stimuli and to inhaled allergens and many chemical mediators (such as histamine, slow reacting substance, kinins) as well as to cholinergic drugs, an increased sensitivity of the subepithelial cough-irritant receptor has been postulated by Nadel.[14] Supporting evidence of this suggestion includes prevention and reversal of both allergen and propanalol-induced bronchospasm with atropine.[15,16]

Chemical Mediators

It has been known for 30 years that histamine is not the only major mediator released from target tissue following an anaphylactic reaction. Brocklehurst, using actively and passively sensitized human tracheal tissue, showed that antihistamines could not block the smooth muscle contracting activity of a compound, now known as slow reacting substance of anaphylaxis (SRS-A), which is formed and released, after antigen stimulation, from contracting guinea pig ileum.[17] Austen and Orange, more recently, demonstrated release of histamine and SRS-A from sensitized human lung fragments following specific allergen challenge.[18] The pulmonary eosinophilic infiltrate associated with some allergic reactions and the blood eosinophilia associated with many may be the result of a newly described mediator—eosinophil chemotactic factor of anaphylaxis (ECF-A).[19] Other possibly important chemical mediators include prostaglandins, particularly the two which have been regularly shown in human lung—PGF_{2alpha} (bronchoconstrictor) and PGE_2 (bronchodilator).[20] Aerosols of PGF_{2alpha} have been shown to be eight thousand times more reactive in the asthmatic lung than in non-asthmatic controls, while histamine shows only a tenfold increase in reactivity in the same situation.[20] PGE_2 has recently been shown to be a more effective bronchodilator in guinea pigs than is isoproterenol.[21]

Release of mediators, particularly histamine and SRS-A from mast cells and basophils is modulated by the autonomic nervous system.[18] Beta-stimulating and other agents which increase intracellular CAMP levels also inhibit release of mediators after allergen-IgE union on the cell membrane. Conversely, drugs which lower intracellular CAMP levels either by beta blockade or alpha stimulation facilitate mediator release. Recently, cholinergic stimuli, probably via the mechanism of stimulation of intracellular cyclic guanosine monophosphate (C GMP) content, have been shown to enhance mediator release; this process is blocked by atropine.[22] Administration of a new pharmacological agent, disodium cromoglycate, also results in inhibition of histamine and SRS-A release, though another mechanism which causes mast cell membrane stabilization is apparently responsible.[23,24]

Immunology

Antibodies

Bronchial asthma is thought to be an example of a Type I hypersensitivity reaction (Gell and Coombs) involving combination of allergen and IgE antibodies on the surface of pulmonary mast cell.[25] This combination results in mediator release which causes bronchial smooth muscle contraction, submucosal edema and increased mucous secretion. Demonstration of mediator release from asthmatic lung tissue in vitro following challenge with appropriate allergen or with anti IgE constitutes direct evidence implicating IgE mediated reactions in the pathogenesis of asthma. Normal lung tissue also releases mediators following passive sensitization with IgE antibodies from allergic serum and challenge with specific allergen.[19] Serum IgE levels are elevated in approximately 60 percent of extrinsic (allergen-induced) asthmatics.[26]

Several studies utilizing fluorescent antibody staining for IgE as well as IgG, IgM and IgA report conflicting results. Callerame et al found a significantly higher deposition of IgG, IgM, IgA and complement (Beta 1C) along the basement membrane in asthmatics (both intrinsic and extrinsic types) than in non-asthmatic controls; the deposits in some cases resembled those found in lupus nephritis.[27] IgE was not detected in basement membrane deposits.[27] Gerber and coworkers,

however, found IgE deposits in the bronchial epithelium, basement membrane and in the bronchial glands, but not on mast cells.[28] IgE was found much less frequently in the non-asthmatic lung.[28] Other immunoglobulins and complement were not found with increased frequency in asthmatic lung tissue.[28] Problems arising out of criteria for type of asthma, drug therapy (particularly steroids), patient selection, and immunologic technique make data comparisons difficult.

Recently, mechanisms other than the classic IgE reaction for asthmatic symptoms have been emphasized and well reviewed.[25,29] In particular, a well-defined syndrome of allergic pulmonary aspergillosis comprising both airway obstruction and pulmonary infiltrates has been described; these patients show evidence of IgE (Type I) and IgG (Type III) hypersensitivity phenomena to Aspergillus fumigatus.[25,29]

Airborne allergens

Until recently it has been assumed that inhaled allergens are brought, with the inspired air, into the airways of the lung and deposited there by direct contact. It has been further thought that these allergens then dissolve in pulmonary tissue fluids and thereby produce their effects upon mast cells and bronchial musculature by local action. These seemingly obvious assumptions are, however, not in agreement with well-established aerodynamic principles concerning the behavior of particles in airstreams.[30] Materials suspended in a moving stream of air, because of their inertia, tend to continue in their original direction, even though the flow of air sharply turns to follow anatomic configurations. This inertial effect produces impaction which, combined with sedimentation, causes larger particles to adhere to the mucosa of areas of changing airflow direction such as the nasopharynx, the oropharynx and areas where airways branch.[30]

The net effect of these physical principles is that deposition of inhaled allergens in the respiratory system is determined by their size. Larger allergens, 20 to 25 micra or larger in diameter, are effectively excluded from the airways and lung, being quantitatively trapped in the nose, mouth and pharynx.[31] It is of interest that this size range includes pollens from essentially all grasses, as well as pollens from many other plants. Since grass pollen clearly causes asthma in sensitive persons, it seems likely that symptoms are produced either by absorption of antigenic material from pollen deposited in the nose, mouth or pharynx or by small fragments of pollen grains that exist freely in nature and may be inhaled deep into the lung.[31,32]

Small airborne particles such as dust (representing, at least partially, fragments of mites), some fungal spores and bits of animal skin (danders) are small enough to be deposited in the airways and lungs during inhalation.[30] It is unlikely that very large pollens, and other potentially antigenic material of similar nature will be inhaled except during very heavy exposure. Such large particles sediment very rapidly in air and therefore are airborne for very short intervals.[31]

Hyposensitization Therapy

In those cases of asthma in which inhalant allergens have been demonstrated to be clinically important, a trial of injection therapy should be attempted.[33] Postulated mechanisms[34] of action include the following:

- *Immunization.* Shortly after the institution of injection therapy, blocking IgG antibodies to the specific allergens used in therapy can be found in the serum. These antibodies prevent allergens from combining with cell-bound IgE by competitive inhibition.
- *Hyposensitization or tolerance.* After an initial rise in IgE, there is a decrease which is slow and may take years to be significantly reduced. Inhibition of IgE synthesis may be on the basis of IgG feedback,[35] or thymic derived lymphocyte (T cell) tollerance[36] which interferes with T cell-B cell interaction probably necessary for IgE antibody synthesis.
- *Change in cell sensitivity.* It has been demonstrated that following injection therapy basophils from allergic persons require increasing amounts of allergen to produce and release 50 percent of cell-bound histamine *in vitro;*[37,38] in some cases no histamine was released regardless of allergen dosage.[39] The mechanism is not clear, but a depletion of intracellular factors necessary for the allergic response may be responsible.[40]

Attempts to correlate cellular and immunological factors with clinical response have not been uniformly successful. In general, it appears that while all these factors change with injection therapy, levels of blocking antibody[41] and degree of cell sensitivity correlate best with therapeutic response.[38] Current research concerned with mechanism of IgE synthesis regulation may reveal

important methods for control of production of those IgE antibodies which result in allergic disease.

Pulmonary Pathophysiology

Site of Obstruction

Classically, the site of obstruction in asthma has been considered as occurring primarily at the bronchiolar level. However, several techniques of measurement have shown that primary source of airway resistance must occur in large airways. This concept has been supported by direct measurements of increased bronchial tone[42] and bronchographic demonstration of constriction in lobar bronchi.[43] Additionally, partitioning of airway resistance between large and small airways has shown that increased airway resistance, characteristic of asthma, is indicative of large airway obstruction.[44]

However, the original concept of obstruction at the small airway level has also been supported by certain recent findings. These include closing volume measurements[45] and the effect of various gases upon maximal expiratory flow volume curves.[46] These latter rather sophisticated measurements have demonstrated beyond doubt that small airways (2 mm in diameter or less) are frequently involved in asthma.[45,46]

The effect of bronchodilator administration may be upon either set of airways. In some cases (mainly those in which airway resistance becomes less) the effect is clearly upon larger airways. In others, mainly those in which closing volumes become less, small airways are dilated.[45] Evidence is accumulating that small airway disease may persist for variable periods even in "asymptomatic" asthma.[45,46]

In summary, it appears that both larger and smaller airways are affected by the asthmatic process and that therapy may beneficially affect either or both sets of airways.

Ventilation/Perfusion ($\dot{V}/\dot{Q}$) Abnormalities

Ventilation/perfusion relationships in asthma are somewhat complex. The manifestations of these abnormalities include hypoxemia and increased diffusing capacity.[47,48]

It has been found that areas of the lungs of many asthmatics, even when relatively asymptomatic, have abnormally decreased ventilation.[47] These abnormalities—both ventilation and perfusion—are reversible with either treatment or time. That is, one area of the lung may be involved one day and on another day a different area of the lung may be involved. The degree of regional ventilatory and perfusion abnormality correlates fairly closely with the severity of disease.

TABLE 2.—*Explanation for Arterial Hypoxemia and Hypocarbia in Asthma**

	Normal	*Asthma*
Mixed venous blood		
PO_2 mmHg	40	41
PCO_2 mmHg	46	41
O_2 content Vol. %	14.5	14.9
CO_2 content Vol. %	53.0	50.5
Arterial blood		
PO_2	95	60
PCO_2	40	36
O_2 content	19.4	18.1
CO_2 content	48.5	46.8
Blood from hypoventilated areas (31.5%)		
PO_2		41
PCO_2		41
O_2 content		14.9
CO_2 content		50.5
Blood from hyperventilated areas (68.5%)		
PO_2		101
PCO_2		33.5
O_2 content		19.6
CO_2 content		45.1

*Arterial and mixed venous blood gas data from studies on a patient with moderate asthma. For sake of simplicity it is assumed that ventilation is essentially zero in 31.5 percent of the lung but that this area is normally perfused. Note that the O_2 and CO_2 contents in arterial blood are a mixture of the gas contents of the hypoventilated and hyperventilated areas; the resulting contents of the mixture then establish the partial pressures observed in arterial blood. The small amount of ventilation/perfusion abnormality seen in the normal supine lung was ignored.

These regional $\dot{V}/\dot{Q}$ abnormalities produce a relative mismatching of ventilation to perfusion in small localized areas throughout the lung.[47] Hence, even though perfusion to an involved area is decreased, ventilation is decreased even more. This imbalance allows some blood to pass through some poorly ventilated areas and therefore not participate in gas exchange. The net effect is that CO_2 is not properly excreted from this blood nor is oxygen properly absorbed by this blood (venous admixture). As the number of these areas increases, total gas exchange is impaired further and hypoxemia becomes worse. On the other hand, arterial carbon dioxide levels (PCO_2) are not elevated, and, in fact, are decreased in asthmatic persons. This apparent paradox is due to the different shapes of the relationship between partial pressures of carbon dioxide and oxygen on the one hand and the content of chemically combined gas in the blood on the other hand (Table 2).

To appreciate the significance of these findings one must understand that the bulk of the lung is

unaffected by regional $\dot{V}/\dot{Q}$ abnormalities in the typical asthmatic patient. This relatively normal lung not only ventilates sufficiently but, apparently in response to the presence of regional abnormalities, in fact, hyperventilates.[47] Therefore, the major portion of the lung is in a state of hyperventilation whereas a small portion of the lung is suffering from the effect of venous admixture. Now, referring to Table 2, one notes that effect of hyperventilation upon carbon dioxide is to lower both the partial pressure of carbon dioxide and the content of carbon dioxide in the blood. The net result of mixing large areas of hyperventilation with small areas of venous admixture results in a situation where hyperventilation predominates and, therefore, arterial PCO_2 is lower. On the other hand, hyperventilation increases the partial pressure of oxygen but does not increase significantly the content of oxygen in the blood. Therefore, arterial PO_2 is decreased since blood which comes from hyperventilated areas of the lung cannot compensate for the low oxygen content of venous admixture blood. Hence, the combined blood will always be lower than normal in oxygen content, and partial pressure of oxygen (PO_2) will be decreased (Table 2).

This type of ventilation/perfusion mismatching is not limited to asthma but may be seen in several other diseases of the lung including bronchitis, pneumonia and pulmonary fibrosis; it is not observed in pure emphysema.[49]

Mechanisms underlying these regional $\dot{V}/\dot{Q}$ abnormalities are not clear. Possible causes include obstruction due to localized brochospasm, local collection of airway mucous, and chance deposition of allergens in particular airways (see above). What causes the perfusion abnormalities is even more obscure. It has been suggested that the regional blood flow abnormalities may be due to local hypoxia, or to increased alveolar pressure, or to local release of vasospasm-causing mediators, or to combinations of these factors. There is evidence that both hypoxemia and vasospastic agents may play roles.[50] The presence of vasospasm is probably beneficial since shunting some of the blood away from the poorly ventilated areas reduces venous admixture and the consequent hypoxemia. Inhaled bronchodilators may cause increased hypoxemia apparently because they are preferentially directed to already well ventilated areas and may increase perfusion generally, thereby increasing relative blood flow to poorly ventilated areas.[51]

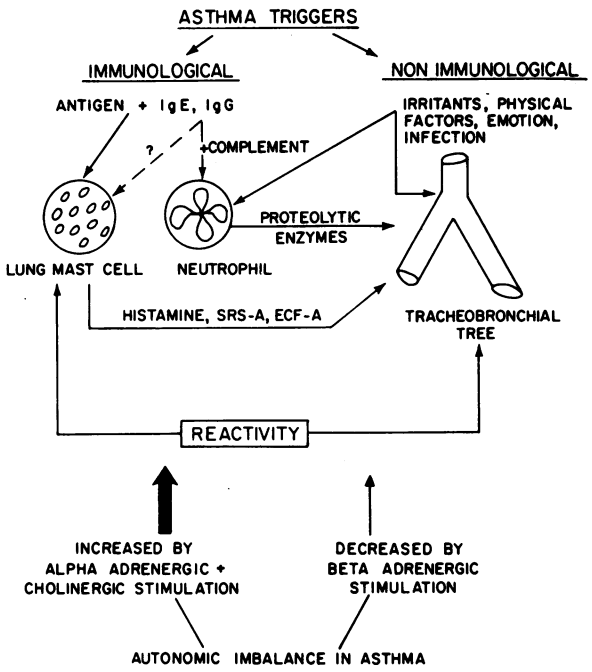

Chart 1.—In bronchial asthma, airway obstruction appears to be the result of non-specific noxious stimuli or immunologic phenomena or both. An attractive hypothesis is that the basic abnormality is an imbalance between factors responsible for relaxation of bronchial smooth muscle and those controlling stability of mast cells. Mediator release may be controlled through maintenance of adequate CAMP levels in these tissues. Agents which lower CAMP or stimulate cholinergic receptors (resulting in elevated intracellular C GMP levels), facilitate bronchial smooth muscle contraction and mediator release.

Single breath diffusing capacity for carbon monoxide (D_LCO) is dependent upon several factors: Reasonable distribution of inspired gas to the alveoli; the presence of blood flow to these alveoli; and a normal membrane between the gas and blood phases. As we have seen in the preceding section, distribution of both ventilation and perfusion are abnormal in asthma; therefore, we might expect *a priori* that D_LCO would be reduced in asthma. However, in fact, D_LCO tends to be increased in asthma about 15 percent more than normal.[48] This paradox can be shown to be due to increased blood flow to the uppermost (apical) regions of the upright lung.[48] This increased blood flow to the upper lung is probably due to increased pulmonary artery pressure.[52] The cause of this probably increased pulmonary artery pressure has not been established. Possible causes include pulmonary vasospasm and increased cardiac output; available evidence favors the former.[48]

The net effect of increased apical blood flow is reduction of the normal high $\dot{V}/\dot{Q}$ relationship pertaining to the upper lung; hence $\dot{V}/\dot{Q}$ matching is more uniform and D_LCO is increased in the apical portions of the lung. Though the presence of low $\dot{V}/\dot{Q}$ areas throughout the lung will reduce D_LCO, increased apical blood flow more than compensates for these low $\dot{V}/\dot{Q}$ areas.[48]

Pulmonary Parenchymal Changes

In the section above, it was noted that asthma may affect the function of the airways and pulmonary blood vessels even during the so-called "asymptomatic" period. It is tacitly assumed that these reactive structures constrict under the influence of chemical mediators, proteolytic enzymes and other pathophysiological stimuli (Chart 1). While the physical interpretation of these reactions is not puzzling, concomitant changes in the pulmonary parenchyma are somewhat surprising.

Lung tissue resistance, though only slightly higher than normal in asthmatic subjects, increased four-fold during provocation of an asthmatic attack by histamine inhalation; simulation of an asthmatic attack by breathing through external resistances did not increase lung tissue resistance.[53] Decreased elastic recoil of the lungs has been demonstrated both during naturally-occurring airway obstruction and for up to two weeks following relief of obstruction by treatment. These changes could not be duplicated by either histamine inhalation or extrathoracic negative pressure.[54] Since the decreased elastic recoil was reversible with time or treatment, it was not due to a destructive process like emphysema. The differing pulmonary parenchymal changes associated with asthma—slightly increased lung tissue resistance increasing after histamine[53] and decreased elastic recoil not changing with histamine[54]—are puzzling and fascinating; these findings need confirmation and simultaneous measurement in the same group of patients.

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